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Novel large-scale synthesis methods for heterocyclic and functionalized boronic acids

INTRODUCTION

Since the development of a wide range of precious metal catalyzed cross coupling reactions and their application in chemical and pharmaceutical synthetic strategies, the demand for suitable precursor materials is growing exponentially. While aryl halides are readily available by well established chemistry, the transmetalation reagents oftentimes appear to be challenging target molecules on their own, especially when it comes to economic large-scale synthesis methods.

As the Suzuki coupling is one of the most commonly applied reactions for the formation of biaryl moieties and employs boronic acids or boronic acid esters as precursors, Archimica has continuously worked on technology development in synthesis and applications of more and more complex boronic acids since twenty years as part of its general R&D focus on differentiating technologies. Especially heterocyclic and highly functionalized derivatives have become a major field within Archimica's research program and a substantial part of Archimica's product portfolio. The required technologies such as cryogenic chemistry, handling of air and moisture sensitive organometallics and ultra-efficient distillation at all scales belong to our main core competences. Literature processes mostly use Grignard- or lithiated reagents as precursors for the synthesis of aromatic boronic acids (1). In many cases, the former are the preferred choice because of their lower prices and better availability. On the other hand, lithium can be introduced in many ways and often allows for the preparation of boronic acids which are not accessible via the Grignard-route. Alternatively, but highly cost intensive, transition metal catalysis provides access to the boronic acid pinacol esters (Figure 1).

Alongside a cost efficient and economic synthesis, purity and assay are playing an important role as well. Common impurities are borinic acids, biphenyls, isomers or simply boric acid and/or water. This is why a tailor-made synthesis for each product from this area has to be developed, for which Archimica both applies improved classical methods as well as completely new pathways. For instance, in a proprietary and generally applicable Archimica process butyllithium could be replaced by more convenient and lower-cost lithium metal in all kinds of lithiations, resulting in the overall conversion of Ar-Hal or Ar-H to the respective boronic acids, with higher selectivity and product purity. This means a reduction in cost and increase in purity at the same time. Several multiton-scale boronic acids are routinely produced at the different Archimica sites, taking advantage of the world's largest cryogenic manufacturing capacity (> 60 m³ of -100°C reactor volume, all FDA-inspected cGMP).

HETEROCYCLIC BORONIC ACIDS

As mentioned above, heterocyclic transmetalation agents and especially boronic acids are of great interest for the manufacturing of pharmaceutically active ingredients (Figure 2). For instance, pyridyl boronic acids have been applied for the synthesis of a series of new GABA-receptor ligands, a powerful class of pharmaceuticals with high potential to treat a large variety of diseases, in that case mental disorders (2). Boronic acids derived from pyridine and quinoline such as **1**, **2**, **3** and **4** have been synthesised at large pilot plant scale (Figure 3; up to 100's of kg).

For the preparation of 4-pyridyl boronic acid **1**, we introduced the hydrochloride of *p*-bromopyridine as precursor material as the bromoarene itself is only of limited stability. In this case, an in situ-lithiation process under cryogenic conditions, typically -75°C, was developed to ensure maximum yields and to minimise by-product formation from typical pyridine side-reactions (Figure 4).

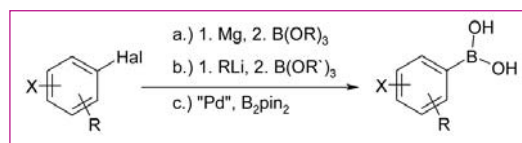


Figure 1. Description of various accesses to boronic acids a) via Grignard chemistry, b) with organolithium compounds, and c) using diborane reagents under cross coupling conditions.

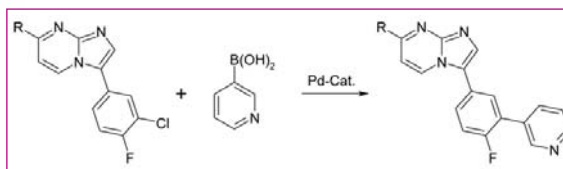


Figure 2. Example for the use of a heterocyclic boronic acid in Suzuki couplings for preparing a series of new GABA_A-receptor ligands.

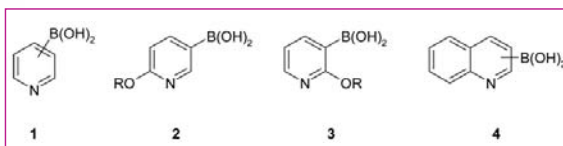


Figure 3. Examples of heterocyclic boronic acids available at technical scale.

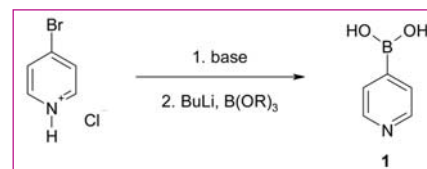


Figure 4. Synthetic scheme for the production of 4-pyridylboronic acid from *p*-bromopyridine hydrochloride.

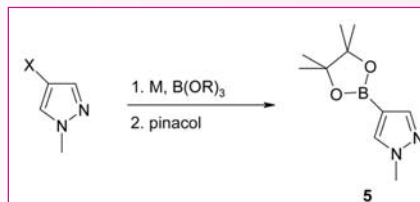


Figure 5. Synthetic scheme for the preparation of 1-Methylpyrazole-boronic acid pinacol ester via halogen metal exchange, reaction with borate, and in situ esterification.

Several derivatives of structural formulas **2-4** have been scaled already as well in high yields. By the above-mentioned in situ-technology, developed by Archimica, not only the listed examples, but also a broad range of N-, S- and O-heterocyclic boronic acids can be produced. In all cases there is no need to use expensive transition metals, costly borane starting materials and also not for continuous processing. Typical yields are >80 percent, and typical product purities are > 99 percent. Inorganic impurities, e.g. lithium and boric acid salts, and organic impurities can be removed easily yielding products with high purities and a high assay. In some cases, the boronic acid itself is instable or the downstream chemistry requires exclusion of the free acid. We have already produced a variety of different esters, usually generated in situ without the need for additional steps and therefore time- and cost-saving.

A striking example for this is the synthesis of 1-Methylpyrazole-boronic acid pinacol ester **5**, performed via metallation of the corresponding halide, reaction with an alkyl borate and in situ esterification with pinacol (Figure 5). The purification follows subsequently by distillation under high vacuum. Due to Archimica's high performance distillation equipment this process can be performed in industrial scale with excellent yields and high product purities.

FUNCTIONALISED AROMATIC BORONIC ACIDS

Oftentimes there is a demand for highly functionalized biphenyls carrying substituents which are unstable towards many usually applied reaction conditions. In addition, the preparation of the corresponding boronic acids with "traditional" technologies might also interfere with these functional groups. The Archimica solution for this challenge consists of two practical processes. The boronic acid group is introduced at first, and in a second step the desired functionality is created without touching the boronic acid function (cf. Figure 6). A prominent example is basing on the 4-formylphenylboronic acid, one of Archimica's largest-scale boronic acids (**3**). The formyl group enables a broad range of reactions building up more complex structures still containing the boronic acid function for coupling reaction later in the process.

By reduction of the carbonyl group, 4-hydroxymethyl phenylboronic acid **7** can be obtained, which is already a standard process at Archimica. The addition of an amine followed by a reducing reagent yields the reductive amination product **8**. Another example is the aldol condensation of the 4-formylphenylboronic acid with ketones yielding π , β unsaturated carbonyl compounds **9** with the boronic acid as an additional functional group. More reactions are currently under investigation.

Boronic acids are also quite stable against oxidative conditions. Archimica has developed a large-scale process oxidising p-tolylboronic acid **10** to p-carboxyphenylboronic acid **11**. Surprisingly, the carbon-boron bond is not affected by the reaction conditions. A newer access to this product consists of the synthesis of the respective cyanophenyl boronic acid **12**, which is then subjected to hydrolysis as shown in Figure 7. By this approach, also Aminocarbonyl phenyl boronic acids **13** are accessible via a new and patented Archimica method (4).

Another approach towards functionalised aromatic boronic acids is the use of protected intermediates as it was done in the case of aminophenyl boronic acid and its pinacol esters **14** (Figure 8) (5). A protective group was added to the amine of haloaniline for this challenging synthesis. Then, the halide was exchanged by boron in the common manner and after hydrolysis of the intermediate the product was isolated by esterification with pinacol and subsequent extraction into the organic phase.

In conclusion, more than 100 different boronic acids have been developed and produced up to a very large scale. In almost all cases, product purities of > 99 percent could be achieved, often even approaching 99.8 percent. By special purification methods, also levels of inorganic impurities are close to detection limits. An interesting trend, especially for pharmaceutical fine chemicals, is that the boronic acids used are getting more and more complex and contain an increasing number of hetero atoms. Despite common needs for very high boronic acid purities, cryogenic technologies have allowed us to realise attractive yields, even for very complex products.

REFERENCES AND NOTES

- D.G. Hall (Ed.), *Boronic Acids. Preparation and Application in Organic Synthesis and Medicine*, Wiley VCH (2005); M. Schlosser (Ed.), *Organometallics in Synthesis*, Wiley (2002).
- W. Li, D. Cai et al., WO03080621.
- A. Meudt, S. Scherer et al., WO0248155.
- A. Meudt, S. Nerdinger et al., WO2007121805.
- C.J. Kressierer, B.W. Lehnemann et al., US2008269523; S. Scherer, A. Meudt et al., US2005038287.

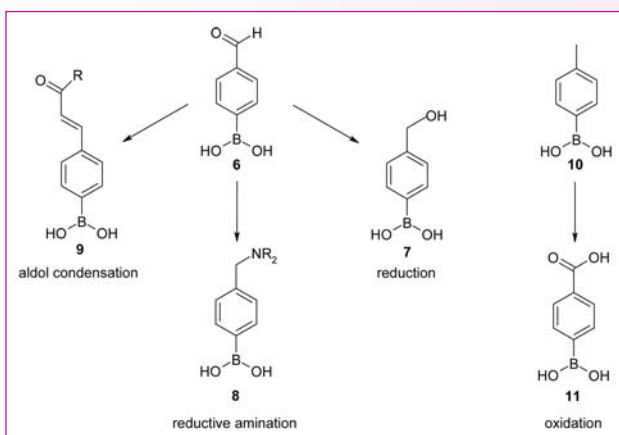


Figure 6. Synthesis of functionalised boronic acids by derivatisation of other suitable boronic acids.

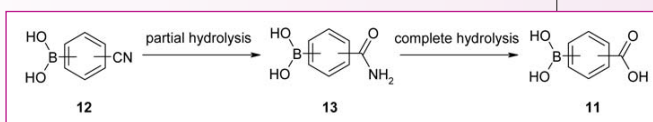


Figure 7. Preparation of Aminocarbonyl phenyl boronic acids and Carboxyphenylboronic acids by hydrolysis of the respective Cyanophenylboronic acids.

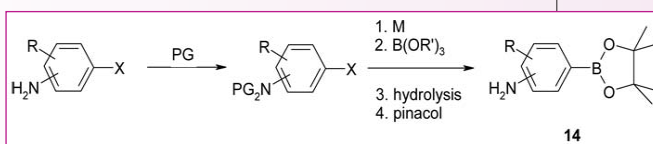


Figure 8. Synthetic scheme for the preparation of Aminophenyl boronic acid pinacol esters starting from readily available haloanilines.

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